Abstract MDS-641

Randomized Phase 1-2 Study to Assess Safety and Efficacy of Low-Dose (LD) Oral Decitabine/Cedazuridine (ASTX727) in Lower-Risk Myelodysplastic Syndromes (LR-MDS) Patients: Interim Safety Analysis

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INTRODUCTION

Hypomethylating agents (HMAs) are standard therapies in higher risk myelodysplastic syndromes (MDS) but appropriate use in lower-risk MDS (Int-1/LR) is less clear

- A prior study of low-dose decitabine (20 mg/m^2 x3 Q28D) vs azacitidine (75 mg/m^2 x 3 Q28D) suggested clinical benefit leading to inclusion in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1]
- A recent randomized study of an oral formulation of azacitidine (CC-486) showed no difference in survival (median overall survival (OS) 17.3 vs. 16.2 months) compared to placebo[2]
  - CC-486 exposure and schedule are different than parenteral azacitidine
  - Survival impacted by early infectious deaths in first 56 days (16 [15%] in CC-486 vs 6 [5.5%] placebo)
- Optimizing dosing regimen for LR-MDS is critical to balance clinical response with risk of myelosuppression

Oral decitabine/cedazuridine (ASTX727)

- Fixed-dose (FDC) combination of 35 mg decitabine (DEC) and the cytidine deaminase (CDA) inhibitor cedazuridine (CED or C) (100mg) produces equivalent pharmacokinetic (PK) AUC exposure compared to intravenous (IV) decitabine[3]
- ASCERTAIN: Phase 3 study led to the approval of oral DEC-C (NCT03306264)
  - The study included some subjects with LR-MDS who received standard dose (SD) ASTX727 for 5 days with clinical benefit[4]

AUC- area under the curve.

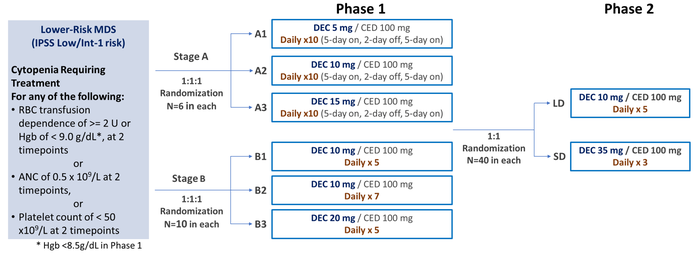
OBJECTIVES

- Identify ASTX727 dose that produces clinical responses while avoiding myelotoxicity in LR-MDS patients who may receive longer term treatment
- Study ASTX727-03 (NCT03502668):
  - Phase 1 investigated multiple dosing regimens of oral DEC-C in LR-MDS to determine RP2D
  - Phase 2 is a randomized comparison of the optimal Phase 1 regimen (10mg DEC / 100mg CED x5, Q28D) vs. an attenuated regimen equivalent to the publication[1] (35mg DEC / 100mg CED x3, Q28D) for LR-MDS

RP2D – recommended phase 2 dose.

METHODS

Figure 1. ASTX727-03 Study Design



Major Entry Criteria:
- Cytopenia requiring treatment
- ECOG PS 0-2
- Adequate organ function
- Prior treatment with HMA is allowed (Phase 1 only)
- Exclude CMML

Primary Endpoint
- Tolerability and Safety (Phase 1)
- Hematologic Response (Phase 2)
  - Hematologic response is defined as hematologic improvement (HI) in 1 or more lineages based on modified 2006 IWG MDS response criteria

Secondary Endpoint
- Safety as determined by incidence of drug-related Grade ≥3 AEs or DLTs (Phase 2)
- Hematologic Response (Phase1)
- RBC and Platelets Transfusion Independence
- PD activity (%LINE-1 methylation change from baseline, HbF induction)
- Decitabine PK parameters
- Overall Survival (OS), Leukemia Free Survival (LFS)

AEs – adverse events; ANC – absolute neutrophil count; CMML – chronic myelomonocytic leukemia; DLTs – dose-limiting toxicities; ECOG – Eastern Cooperative Oncology Group; IPSS – International Prognostic Scoring System; Int – intermediate; IWG – International Working Group; NE – not evaluated; PS – performance status; RBC – red blood cell; RP2D – recommended phase 2 dose.

RESULTS

Table 1. Patient Demographics/Characteristics

Characteristics		Phase 1 (N=47)	Phase 2 LD (N=40)	Phase 2 SD (N=41)
Age in years (median, range)		76 (51-88)	70 (53-87)	75 (57-86)
Sex: Male/Female, n (%)		30 (65) / 17(35)	25 (63) / 15 (37)	30 (73) / 11 (27)
ECOG PS	0 / 1 / 2	10 (21)/34 (72)/3(6)	10 (25)/27(68)/3(7)	12 (30)/27(66)/2(5)
IPSS risk classification	Low-risk / Int-1	15 (32) / 32 (68)	10 (25) / 30 (75)	13 (32) / 28 (68)
IPSS-R risk classification*	Very Low / Low Intermediate High / Very high	0 / 17 (52) 12 (36) 4 (12) / 0	0 / 19 (48) 16 (40) 5 (12) / 0	2 (5) /22 (54) 15 (36) 2 (5) / 0
	Score 3.5 >= / 3.5 >	23 (70) / 10 (30)	24 (60) / 16 (40)	29 (71) / 12 (29)
IPSS-M risk classification*	Very Low / Low ML** / MH** High / Very High	0 / 5 (15) 7 (21) /11 (33) 9 (27) / 1 (0.3)	NA	NA
IPSS cytogenetics risk	Good/Intermediate/Poor	33 (70)/8 (17)/4 (9)	30 (75)/9 (22)/1 (3)	33 (81)/6 (15)/1 (2)
Prior treatment for MDS		27 (57)	19 (48)	22 (54)
	ESA	16 (34)	9 (23)	8 (20)
	Lenalidomide	13 (28)	0	6 (15)
	Luspatercept	1 (2)	10 (25)	8 (20)
	Parenteral HMAs	13 (28)	0	0
Bone Marrow Blasts (%, range)		2 (0-8)	3 (0-7)	2 (0-10)
RBC Transfusion Dependence, n (%)		21 (45)	19 (48)	23 (56)
Platelet Transfusion Dependence, n (%)		3 (6)	3 (8)	7 (17)

*N=33 **ML / MH: Moderate Low/ Moderate High

Table 2. Study Treatment Exposure

	Phase 1 (N=47)	Phase 2 LD (N=40)	Phase 2 SD (N=41)
Number of cycles			
Median	9.0	7.0	7.0
Min, Max	1, 41	1, 27	1, 22
At least one delayed cycle, n(%)	36 (76.6)	25 (62.5)	32 (78.0)
At least one dose-reduced cycle, n (%)	26 (55.3)	10 (25.0)	13 (31.7)

Median follow up

Phase 1: 37.7 months (Min–Max: 0.9-49.7)
Phase 2: 11.0 months ((Min–Max: 0.8-25.4)

Table 3: Phase 1 Dose Limiting Toxicity (DLT)

Stage	Ph1 Stage A			Ph1 Stage B		
Cohort	A1	A2	A3	B1	B2	B3
Regimen	5mg 10-day	10mg 10-day	15mg 10-day	10mg 5-day	10mg 7-day	20mg 5-day
DLT / Evaluable subject #	3/10	4/4	-	3/11	7/10	7/11

Table 4: Safety Results: TEAE in >20% of Patients (Independent of Attribution)

MedDRA Preferred Term	Phase 1 (N= 47)		Phase 2 LD (N = 40)		Phase 2 SD (N = 41)	
	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Subjects with any TEAE	47 (100)	45 (95.7)	39 (97.5)	30 (75.0)	41 (100)	36 (87.8)
Total number of TEAEs	1023	304	483	146	617	163
Fatigue	21 (44.7)	1 (2.1)	9 (22.5)	0	16 (39.0)	1 (2.5)
Neutrophil count decreased	18 (38.3)	17 (36.2)	12 (30.0)	11 (27.5)	13 (31.7)	13 (31.7)
Anaemia	16 (34.0)	13 (27.7)	12 (30.0)	9 (22.5)	12 (29.3)	11 (26.8)
Platelet count decreased	11 (23.4)	9 (19.1)	13(32.5)	9 (22.5)	15 (36.6)	13 (31.7)
Constipation	16 (34.0)	1 (2.1)	9 (22.5)	0	10 (24.4)	1 (2.4)
Headache	8 (17.0)	0	9 (22.5)	0	9 (22.0)	1 (2.4)
Nausea	10 (21.3)	0	10 (25.0)	0	7 (17.1)	0
Neutropenia	19 (40.4)	17 (36.2)	7 (17.5)	6 (17.5)	9 (22.0)	9 (22.0)
Oedema peripheral	12 (25.5)	0	6 (15.0)	0	10 (24.4)	0
WBC count decreased	8 (17.0)	8 (17.0)	7 (17.5)	0	9 (22.0)	0
Corona virus infection	6 (12.8)	1 (2.1)	2 (5.0)	0	9 (22.0)	1 (2.4)

TEAE - Treatment-Emergent Adverse Event; WBC – white blood cell

Table 5: Death Events (Any Cause)

Reason for Death	Phase 1 (N=47)	Phase 2 LD 10mg 5-day (N=40)	Phase 2 SD 35mg 3-day (N=41)
Total, n (%)	25 (53.2)	9 (22.5)	7 (17.0)
Disease Progression	10 (21.3)	5 (12.5)	3 (7.3)
AE	4 (8.5)	1 (2.5) (myocardial infarction)	1 (2.4) (infection*)
Unknown	7 (15.0)	2 (5.0)	1 (2.4)
Other	4 (8.5)	1 (2.5)	2 (4.8)

*Admitted C1D14: febrile neutropenia (no prophylactics), pseudomonas infection (related fatal SAE). Passed away 22 days post-last dose of ASTX727

Early Death
Within 30 days: n=2 in Phase 1 and n=1* in SD arm
Within 60 days: n=1 in SD arm

Figure 2: Phase 2 Counts Mean Ratio Changes from Baseline

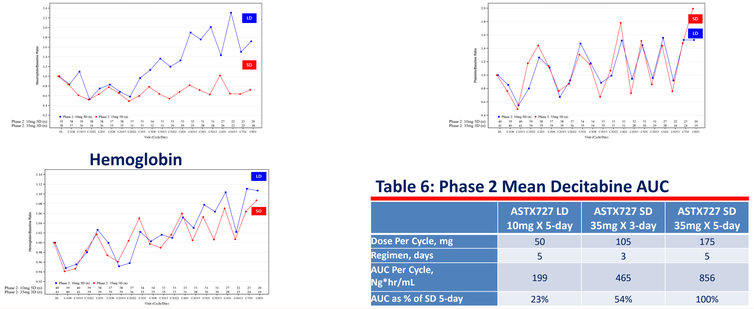


Table 6: Phase 2 Mean Decitabine AUC

	ASTX727 LD 10mg X 5-day	ASTX727 SD 35mg X 3-day	ASTX727 SD 35mg X 5-day
Dose Per Cycle, mg	50	105	175
Regimen, days	5	3	5
AUC Per Cycle, Ng*hr/mL	199	465	856
AUC as % of SD 5-day	23%	54%	100%

RESULTS

Table 7: Phase 1 Efficacy Results: Transfusion Independence (TI)

	Phase 1
RBC TD at baseline (>2U within 8 weeks), n	23
Post treatment RBC TI, n (%)	11 (47.8)
TI duration, median Months (95%CI)	11.5 (2.3, NE)
Time to TI, median Months (Min, Max)	2.4 (0.7, 22.6)
Platelet TD at baseline, n	3
Post-Treatment Platelet TI, n (%)	1 (33.3)

Figure 3: Phase 1 Efficacy Results: Swimmer plot of RBC Transfusion

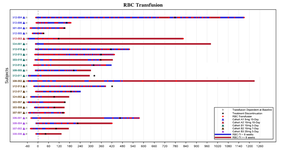


Figure 4: Phase 1 Kaplan-Meier Curves of Overall Survival (N=47)

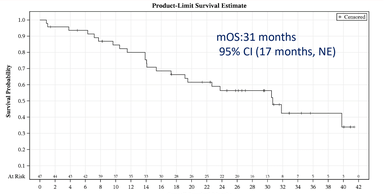
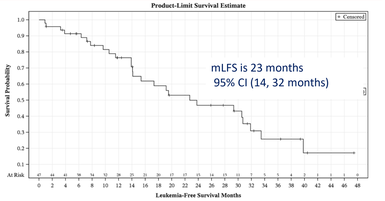


Figure 5: Phase 1: Kaplan-Meier Curves of Leukemia Free Survival (N=47)



mOS – median overall survival; mLFS – median leukemia-fee survival; TD – transfusion-dependence.

SUMMARY & CONCLUSIONS

SUMMARY

Phase 1: Investigation of oral administration of various low-dose DEC-C regimens in LR-MDS showed:
- Safety profile consistent with standard dose of DEC-C
  - Treatment-emergent events mostly related to myelosuppression
  - Cohorts with lower doses/shorter dosing regimen had less neutropenia
  - No clinically significant gastrointestinal adverse effects
- All dosing cohorts demonstrated clinical activity
  - 11/23 patients became RBC transfusion-independent for at least 8 weeks; mOS 31 months
  - ➢ Dose schedule 10 mg DEC/100 mg CED daily X 5 days (Cohort B1) was selected as the RP2D based on tolerability & safety profile and maintained clinical activity

Phase 2: Compared 81 LR-MDS subjects on RP2D (10mg DEC/100mg CED (LD) for 5 days) from Phase 1 vs 35mg DEC/100mg CED (SD) for 3 days
- IPSS INT-1 risk: 75% (LD) & 68% (SD); IPSS-R risk score ≤3.5: 60% (LD) & 70% (SD)
- Median of 7 treatment cycles; 12 subjects discontinued for bone marrow transplant (after median of 5 treatment cycles with range: 1-10)
- The pharmacokinetics of decitabine were linear and proportional, as LD decitabine total cycle AUC $_{0\text{-}24H}$ was about half of the SD 3-day exposures, and approximately 25% of the SD 5-day exposures
- Two early deaths associated with infectious sequelae of myelosuppression in SD arm, but none in LD arm
- No significant safety differences between arms
- Reduced neutropenia in LD 5-day arm; stable/improved blood cell counts across all lineages

CONCLUSIONS

This Phase 1/2 study shows that a LD 5-day treatment regimen is tolerable with less neutropenia, suggesting that it may be an optimal regimen for LR-MDS provided that longer term efficacy results prove to be comparable to the SD 3-day regimen.

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3. Savona, et al. Blood (2020) 136 (Supplement 1): 37–38.
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CONTACT INFORMATION

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